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Isoniazid Chemoprophylaxis of Tuberculosis

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■ *A major step toward the eradication of tuberculosis in the United States has been the use of isoniazid for chemoprophylaxis in certain persons who have positive tuberculin skin tests but no other evidence of active infection. Chemical trials have demonstrated the effectiveness of chemoprophylaxis in groups where there is a relatively high risk of active tuberculosis. However, only the practicing physician can identify and offer chemoprophylaxis to many other susceptible persons. Even if the patient is a candidate for isoniazid, the risk of developing tuberculosis must be weighed against the cost and possible adverse effects of the drug. If isoniazid is given, the physician must be alert to the signs of possible drug toxicity. If isoniazid is not given, he must anticipate the development of active tuberculosis in susceptible persons.*

CHEMOPROPHYLAXIS IN TUBERCULOSIS generally refers to the use of Isoniazid (INH) to prevent tuberculous infection or its manifestations. Primary prophylaxis refers to giving INH to persons not yet infected with tuberculosis or to those who are presumably infected but who have not yet developed delayed hypersensitivity. Secondary prophylaxis refers to giving INH to persons with positive tuberculin skin tests who do not have clinically active disease. This is the chief concern of this paper. We have summarized the toxicity of INH, the successful results of chemoprophylaxis trials, and the relative risk of developing tuberculosis, so that the physician can decide in an individual case if INH should be given.

An ideal chemoprophylactic agent should be easy to administer, effective in preventing disease, cheap, and non-toxic.[1] Isoniazid is easy to administer to children and adults. The total cost of administering INH for one year is eighty dollars—infinitely less than the cost of prolonged treatment in hospital for active tuberculosis.[2] Although unusual, some undesirable effects have been attributed to INH. The drug may induce a syndrome similar to systemic lupus erythematosus or rheumatoid arthritis.[3-6] It increases the cumulative effects of diphenylhydantoin (Dilantin®).[7] Drug resistance has been reported but is very rare in chemoprophylaxis.[8] Although only rarely serious, liver toxicity has occurred,[9,10] and isoniazid chemoprophylaxis should be deferred

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TABLE 1.—*Tuberculosis Case Rate per 1000 During Medication Year and Subsequent Followup Years in* INH *and Placebo Groups*[13]

	Medication Year		*Followup Years*		*Time of Followup*
	Placebo	INH	*Placebo*	INH	
Primary TB (children) 2,750 Cases*	22.9	1.4	7.0	2.2	8 years 70% followup
Contacts of Active TB 27,847 Cases	6.2	1.4	16.2	7.4	10 years 98% followup
Mental Institution Patients** 25,210 Cases	1.7	0.2	7.4	3.4	10 years 94% followup
Alaskan Villagers 6,064 Cases	15.2	5.3	30.8	13.8	6 years nearly 100% followup
Adults with inactive TB never previously treated 1,992 Cases	18.0	9.1	45.0	16.1	5 years 97.8% followup

*This includes children with normal x-rays, paratracheal or hilar node enlargement and parenchymal involvement.
**These patients were treated regardless of whether the skin test was negative or positive.

in the presence of active liver disease.[11] Impairment of memory has been reported[12] but is definitely not significant[2,13] and INH does not adversely affect epilepsy.[13] Peripheral neuropathy is not a problem with the dose used for chemoprophylaxis unless there is associated malnutrition or alcoholism, in which case pyridoxine should be added. Other mild reactions occur in about one percent of patients;[14] however, the incidence is much smaller in children.[2] The effectiveness of INH in reducing the incidence of tuberculosis has been demonstrated particularly well in the United States Public Health Service Clinical Trials summarized below. These studies are the basis for recommending INH chemoprophylaxis in the United States today.

Animal Trials

In 1953, Ferebee and Palmer[15] treated guinea pigs with isoniazid, 5 mg per kg of body weight per day, for one month before and for two and one half months after large innoculations of virulent tubercle bacilli. At the end of 26 weeks these animals had survived and maintained normal growth patterns whereas the control animals had died. Then, experimentally infected mice and guinea pigs were treated with INH, beginning on the day of injection, for six weeks. One-hundred percent protection was achieved at eight months relative to controls.[16] In these and other animal studies[17] the efficacy of INH in preventing tuberculosis was related to (1) the size of the infective dose, (2) the time between infection and the initiation of treatment (a delay of over fourteen days resulted in poorer results at a given dose), (3) the duration of therapy (the minimal period for effective therapy was 12 weeks). In another study, monkeys were inocculated with bacilli and at the same time were given INH for the following four to six months. One year later all the monkeys had negative skin tests, suggesting that true infection has actually been prevented.[18] Thus in animals INH was effective for primary prophylaxis in doses as small as 3 mg per kg per day if administered within two weeks of the onset of infection and for a period of at least three months. These studies were the basis for the trials of chemoprophylaxis in clinically-well humans who, because of a positive tuberculin skin test, were presumed to have been exposed to, if not infected with, M. tuberculosis.

Clinical Trials

The benefit of INH prophylaxis was then demonstrated in clinical trials by the United States Public Health Service in patients with no clinical evidence of active disease. The trials are summarized in Table 1.

The participants were given INH, approximately 5 mg per kg of body weight per day, or a placebo in double blind fashion to take for one year. X-ray films of the chest were taken at the beginning of the trial and at the end of the medication year. The results are tabulated in terms of case rates of active tuberculosis per 1,000 in placebo and INH groups both during and after the medication year.

The most striking reduction in morbidity from tuberculosis occurred in children with positive skin tests without other evidence of active disease. There was a reduction of 94 percent in the INH group compared with controls during the

medication year and a reduction of 70 percent thereafter. Curry[2] reported even more dramatic results in San Francisco school children. There was one case of tuberculosis in 2910 children with positive tuberculin reactions who took INH and 25 cases in 1192 children who did not take INH. One reason for the good results in this study appears to have been the careful follow-up of patients during the medication year to ensure that they took the drug.

In household contacts of newly diagnosed cases of tuberculosis and in the trial in the Alaskan villagers one can see, in Table 1, not only the high risk of developing tuberculosis in these populations but also the beneficial effect of INH relative to controls in preventing active disease during and after the medication year. In mental institutions there was a lower overall risk of developing disease but a similar reduction in active cases in the INH group.

The last group in Table 1 included adults who had never been treated with anti-tuberculosis drugs but who had x-ray evidence of "old" or "inactive" disease—namely fibrotic apical lesions or more extensive disease which had not changed for several years. These patients had a high risk of developing active disease, as seen in the case rate of 18.0 cases per thousand in the placebo group (a case rate similar to that in Alaskan Eskimo villages) as opposed to 9.1 cases per 1000 for those given INH. There seems to be little doubt that INH chemoprophylaxis was worth while in these selected populations.

This last group of "inactive" untreated cases deserve particular attention. First, about 80 percent of the new active cases in the United States occur in people with "endogenous" infection—that is, clinically inapparent disease for over one year.[24-26] Obviously if these patients could be found and treated with INH before active tuberculosis developed, there would be a major reduction in the number of new active cases. Second, since these patients in whom active tuberculosis develops are the principal source of exposure for previously uninfected persons, the logical emphasis for chemoprophylaxis should be in this group. Thus, the Public Health Service has emphasized the eradication of the chief source of new cases and reservoir of infection rather than BCG vaccination of tuberculin-negative (and therefore uninfected) persons who represent only 20 percent of the new cases. The Public Health Service feels it is easier in the United States to try to identify and treat the reservoir than to vaccinate the huge number of uninfected persons.

Discussion—
Who to Treat with INH for One Year

It is impractical to attempt to skin test and take x-ray films of everyone in the United States, treating all clinically inactive cases with INH for one year and all active cases with additional therapy, desirable as this would be. However, the high-risk groups should be identified and treated, and the Public Health Service data provide information for identifying them.

Obviously, close contacts of persons with active tuberculosis are at high risk and should be treated after appropriate cultures if their skin test converts and should be followed closely, as with any person whose skin test becomes positive. Certain stress factors are associated with a significant risk of developing active tuberculosis in people with positive skin tests. Many of these patients are seen frequently by physicians and the tuberculin status should be known so that INH can be offered to the tuberculin-positive persons. Alcoholism and malnutrition are associated with poor host resistance to tuberculosis. Gastric resection, which many of these patients have had, is also a predisposing factor. Other groups with poor resistance to infection are those with diabetes (particularly if severe and out of control), and those with an impaired immune mechanism. This latter group means not only those with myeloproliferative disorders, but also those being treated with corticosteroids or other immunosuppressive agents. Pregnancy and silicosis also are associated with a high risk of development of the disease.

In the general population, where the principal reservoir of the disease is, the chief high-risk-identifying factors are (1) the infection status judged by the skin test and (2) the presence of abnormalities on chest x-ray studies even though interpreted as inactive. Foremost, a recent conversion to positive reaction in a person known to be tuberculin-negative previously indicated a risk of 5 to 15 percent that clinically active tuberculosis would develop.[27] This is a definite indication for INH after cultures are taken.

Likewise, the presence of x-ray abnormalities, even though interpreted as inactive, greatly increases the risk. In patients in mental institutions

with tuberculin skin tests greater than 10 mm induration, the presence of an abnormal (but "inactive") chest x-ray altered the statistical chance of developing active tuberculosis from 0.11 percent, which is quite insignificant, to 1.31 percent.[22] Adults who have never had chemotherapy for tuberculosis and who have inactive disease on clinical and radiological grounds have a tuberculosis morbidity rate of about 2 percent per year. In trials with INH "prophylaxis" in these people, the morbidity rate was about 1 percent during the year of chemoprophylaxis, a reduction of 50 percent. Furthermore, the administration of INH for one year reduced the chances of developing active disease in subsequent years from a value of 4.5 percent in the control group to 1.6 percent in the group who had had INH for a year.[13] Most of these patients have been followed for ten years. This opportunity for preventive treatment must be extended to this group of adults with positive skin tests and "inactive" tuberculosis on clinical radiological grounds because 80 percent of the new active cases came from this reservoir.[25-27] An alternative of mass bacille Calmette Guerin (BCG) vaccination, which is done in tuberculin negative persons, would not affect this population which is the chief source of new cases.

Conclusions

It seems appropriate to restate the groups who require chemoprophylaxis (300 mg INH per day for one year for adults) based on the recommendations of the United States Public Health Service and the American Thoracic Society.[28]

1. Persons who are known to have recently converted their skin test.
2. Persons who have had active tuberculosis in the past and have had no drug therapy or inadequate therapy.
3. Persons with healed adult-type pulmonary tuberculosis and a positive skin test.
4. Certain clinical situations in patients with positive skin tests:
   (a) Patients receiving corticosteroid or immunosuppressive therapy
   (b) Patients undergoing a partial gastrectomy
   (c) Patients with lymphoma or leukemia
   (d) Patients with severe diabetes
   (e) Patients with silicosis
   (f) Patients in the last trimester of pregnancy*
5. Household contacts of active cases if the contact has a positive skin test.
6. Patients under age 20 years who have positive skin tests.

There are two other categories of patients where the indications are not as clear: (1) persons over age 20 years with positive skin test (not recent converters) and normal chest x-ray films (these patients have a risk of about 0.11 percent per year of developing active tuberculosis,[22] and (2) persons with clinical conditions where the skin test is unreliable or who are receiving steroid or immunosuppressive therapy. This risk of developing tuberculosis in the latter group is not known but it is undoubtedly increased. The incidence of untoward effects from INH is about 1 percent at the usual doses,[14] and although most of these effects are minor they must be considered in treating patients with a relatively small chance of developing tuberculosis anyway, such as those over 20 years of age with normal chest x-ray films and positive skin tests for many years. It is imperative to know the tuberculin status of patients in these high risk groups. Any physician who treats tuberculosis sees tragic but preventable cases in which skin testing was not done and chemoprophylaxis was not even thought of. Even if a physician elects not to use INH in high risk patients, the awareness of the risk of developing tuberculosis is the physician's responsibility. This is especially important with the increasing use of corticosteroids and immunosuppressive agents. The least the practicing physician can do is to give the benefit of chemoprophylaxis to his own patients whenever it is indicated.

REFERENCES

1. Lambert HP: The chemoprophylaxis of tuberculosis, a review. Am Rev Resp Dis 80:648-658, Nov 1959
2. Curry FJ: Prophylactic effect of isoniazid in young tuberculin reactors. N Engl J Med 277:562-567, Sep 1967
3. Siegel M, Lee SL, Peress NS: The epidemiology of drug-induced systemic lupus erythematosus. Arthritis Rheum 10:407-415, Oct 1967
4. Hothersoll TE, Mowat AG, Duthie JJ, et al: Drug induced lupus syndrome. A case report implicating isoniazid. Scott Med J 13:245-247, Jul 1967
5. Saslaw S, Klainer AS: Rheumatoid syndrome during isoniazid therapy. Am Rev Resp Dis 100:221-223, Aug 1969
6. McKusick AB, Hsa JM: Clinical and metabolic studies of the shoulder hand syndrome in tuberculosis patients (abstract). Arthritis Rheum 4:426, Aug 1961
7. Kutt H, Brennan R, Dehejia H, et al: Diphenylhydantoin intoxication—A complication of isoniazid therapy. Am Rev Resp Dis 101: 377-384, Mar 1970

*There is absolutely no evidence that INH has a detrimental effect on pregnancy if given before or during the pregnancy.[13] However, since the number of patients studied is small (581), it seems reasonable to recommend prophylaxis only during and after the last trimester.

8. Kapur VN, Gillespie DG, Wolinsky E: Drug resistant tubercle bacilli from a patient with inactive disease on INH prophylaxis study. Am Rev Resp Dis 94:94-96, Jul 1966

9. Martin CE, Artland JB: Hepatitis after isoniazid administration. N Engl J Med 282:433-434, Feb 1970

10. Scharer L, Smith JP: Serum transaminase elevations and other hepatic abnormalities in patients receiving isoniazid. Ann Intern Med 71:1113, 1120, Dec 1969

11. Summary of the *ad hoc* advisory committee on isoniazid and liver disease in Morbidity and Mortality. U.S. Department of Health, Education and Welfare 20:231-234, Jul 3, 1971

12. Tørning K, Olsen PZ: Isoniazid and impairment of memory. Dis of the Chest 53:675-678, Jun 1968

13. Ferebee SH: Controlled chemoprophylaxis trials in tuberculosis. A general review. Bibl Tuberc 26:28-106, 1970

14. Goodman LS, Gilman AC (Eds): The Pharmacological Basis of Therapeutics. 3rd Ed, The Macmillan Co., New York, 1966, p 1324

15. Ferebee SH, Palmer CE: Prevention of experimental tuberculosis with isoniazid. Am Rev Tuberc 73:1-18, Jan 1956

16. Palmer CE, Ferebee SH, Hopwood L: Studies on prevention of experimental tuberculosis with isoniazid.—II. Effects of different dosage regimens. Am Rev Tuberc 74:917-939, Dec 1956

17. Peizer LR, Chaves AD, Widelock D: The effects of early isoniazid treatment in experimental guinea pig tuberculosis. Am Rev Tuberc 76:732-751, Oct 1957

18. Schmidt LH: International symposium on the Deborah Sanatorium and Hospital—Panel I, Chemoprophylaxis of tuberculosis. Am Rev Resp Dis 80:Number 4, part 2 p 1-139, Oct 1959

19. Lincoln EM: The effect of antimicrobial therapy on the prognosis of primary tuberculosis in children. Am Rev Tuberc 69:682-689, May 1954

20. Ferebee SH, Mount FW: Tuberculosis morbidity in a controlled trial of the prophylactic use of isoniazid among household contacts. Am Rev Resp Dis 85:490-510, Apr 1962

21. Mount FW, Ferebee SH: The effect of isoniazid prophylaxis on tuberculosis morbidity among household contacts of previously known cases of tuberculosis. Am Rev Resp Dis 85:821-827, Jun 1962

22. Ferebee SH, Mount FW, Murray FJ, et al: A controlled trial of isoniazid prophylaxis in mental institutions. Am Rev Resp Dis 88:161-175, Apr 1963

23. Comstock GW, Ferebee SH, Hammes LM: A controlled trial of community-wide isoniazid prophylaxis in Alaska. Am Rev Resp Dis 95:935-943, Jun 1967

24. Ferebee SH, Palmer DE (Editorial). The epidemiologic bonus. Am Rev Resp Dis 91:104-107, Jan 1965

25. Ferebee SH: Speech presented May 24, 1966 at the National Tuberculosis meeting held in San Francisco, California

26. Stead WW: Pathogenesis of a first episode of chronic pulmonary tuberculosis in man—Recrudescence of residuals of the primary infection or exogenous reinfection. Am Rev Resp Dis 95:729-745, May 1967

27. American Trudeau Society: Treatment of the adult tuberculin converter—A statement by the committee on therapy. Am Rev Resp Dis 81:443-445, May 1960

28. Chemoprophylaxis for the prevention of tuberculosis—Report of the ad hoc committee on chemoprophylaxis. Am Rev Resp Dis 96:558-560, 1967

STEROIDS IN OPTIC NEURITIS

We feel that optic neuritis is a form of cerebral edema. We feel that steroids used in proper dosage are definitely effective, and that the effect is dose-related and dose-related at massive dose levels, not at the standard levels. We feel steroids are effective because of the immediate effect on pain. This is within 12 hours. You can start the patient at night, as we usually do, and have improvement manifested the following morning. So we are talking about less than 24 hours in most of these patients. You can see the efficacy of steroids in the effect on pain, visual acuity, visual field, color function, and in the appearance of the disc.

You should treat with high doses of steroids—50 mg of prednisone immediately and 25 mg of prednisone every four hours for six doses. We think that patients should be treated for approximately 36 hours and then re-evaluated for an idea of how long treatment should continue. You may be able to stop treatment in 36 hours and certainly in 72 hours. . . . There is no benefit at all from prolonged treatment with steroids. . . .

What we aim to do is abort the acute attack of optic neuritis in the same way that the neurosurgeon aims to remove cerebral edema after a brain contusion or concussion. We want to minimize the residual effects because it is those effects which tend toward progressive optic atrophy and eventually loss of vision, and determine the life cycle of that patient's optic nerve.

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